

1. (Previously presented) A method of improving gene therapy by increasing the level of expression of a recombinant protein *in vivo* in cells of an individual, wherein the protein is expressed from an expression vector which has been introduced into the cells, which method comprises administering to the individual an active site-specific chaperone of the protein.

2. (Original) The method of claim 1, wherein the vector is a viral vector.

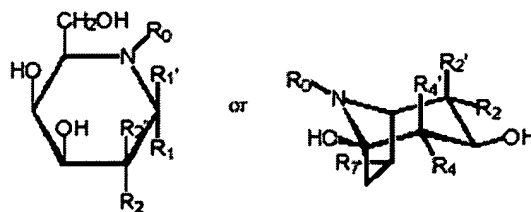
3. (Original) The method of claim 2, wherein the viral vector is an adenoviral vector.

4. (Original) The method of claim 1, wherein the protein is an enzyme and the active site-specific chaperone is a reversible competitive inhibitor of the enzyme.

5. (Original) The method of claim 4, wherein the enzyme is  $\alpha$ -galactosidase A.

6. (Withdrawn) The method of claim 4, wherein the enzyme is  $\beta$ -glucocerebrosidase.

7. (Original) The method of claim 5, wherein the reversible competitive inhibitor is a compound of the following formula:



wherein  $R_0$  represents H or a  $C_1$ - $C_{12}$  alkyl chain;

$R_1$  and  $R_1'$  independently represent H, OH, a 1-4 carbon alkyl, alkoxy or hydroxyalkyl group;

$R_2$  and  $R_2'$  independently represent H, OH or a  $C_1$ - $C_{12}$  alkyl group

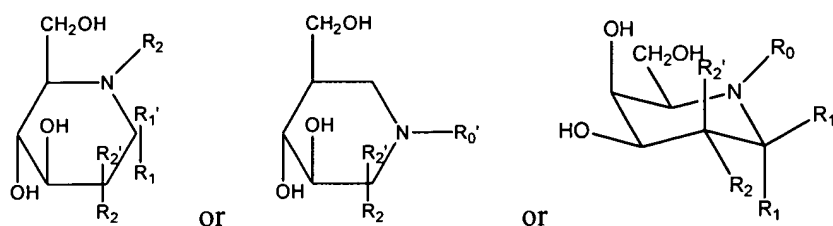
$R_4$  and  $R_4'$  independently represent H, OH; and

$R_7$  represents H or OH.

8. (Original) The method of claim 7, wherein the reversible competitive inhibitor is a compound selected from the group consisting of 1-deoxygalactonojirimycin,  $\alpha$ -*allo*-homonojirimycin,  $\alpha$ -*galacto*-homonojirimycin,  $\alpha$ -1-C-butyl-deoxynojirimycin, calystegine A<sub>3</sub>, calystegine B<sub>2</sub>, N-methyl-calystegine A<sub>3</sub>, and N-methyl-calystegine B<sub>2</sub>.

9. (Original) The method of claim 7, wherein the reversible competitive inhibitor is 1-deoxygalactonojirimycin.

10. (Withdrawn) The method of claim 6, wherein the reversible competitive inhibitor is a compound of the following formula:



wherein  $R_0$  represents H or a  $C_1$ - $C_{12}$  alkyl chain;

$R_0'$  represents H, a straight chain or branched saturated carbon chain containing 1-12 carbon atoms, optionally substituted with a phenyl, hydroxyl or cyclohexyl group;

$R_1$  and  $R_1'$  independently represent H, OH, a 1-4 carbon alkyl, alkoxy or hydroxyalkyl group; and

$R_2$  and  $R_2'$  independently represent H, OH or a  $C_1$ - $C_{12}$  alkyl group.

11. (Withdrawn) The method of claim 10, wherein the reversible competitive inhibitor is a compound selected from the group consisting of isofagomine, N-dodecyl-isofagomine, N-nonyl-isofagomine, N-dodecyl-deoxynojirimycin, calystegine A<sub>3</sub>, calystegine B<sub>2</sub>, calystegine B<sub>3</sub> and calystegine C<sub>1</sub>.

12. (Withdrawn) The method of claim 11, wherein the reversible competitive inhibitor is isofagomine.

13. (Withdrawn) The method of claim 11, wherein the reversible competitive inhibitor is N-dodecyl-isofagomine.

14. (Previously presented) A method of improving gene therapy by increasing the level of expression of a recombinant protein *in vivo*, wherein the protein is expressed by host cells comprising an expression vector encoding the protein, which method comprises co-administering to the individual the host cells and an effective amount of an active-site specific chaperone of the protein.

15. (Original) The method of claim 14, wherein the vector is a viral vector.


16. (Original) The method of claim 15, wherein the viral vector is an adenoviral vector.

17. (Original) The method of claim 15, wherein the host cells are human primary cells and the individual is a human.

18. (Original) The method of claim 17, wherein the human cells are mesenchymal stem cells.

19. (Original) The method of claim 14, wherein the protein is an enzyme.

21. (Withdrawn) The method of claim 19, wherein the enzyme is  $\beta$ -glucocerebrosidase.

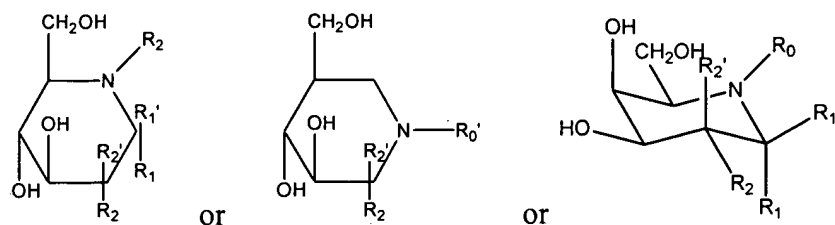

  
 The left structure is a piperidine ring with a hydroxyl group (HO) at position 3, a hydroxymethyl group (CH<sub>2</sub>OH) at position 4, and a nitrogen atom (N) at position 1. Substituents R<sub>0</sub>, R<sub>1</sub>, R<sub>1</sub>', R<sub>2</sub>, and R<sub>2</sub>' are attached at positions 1, 2, 3, 4, and 5 respectively. The right structure is a bicyclic isomer, specifically a 3,4-dihydro-2H-pyrido[1,2-b:3',4'-d]pyrazole derivative, with substituents R<sub>0</sub>, R<sub>1</sub>, R<sub>2</sub>, R<sub>2</sub>', R<sub>4</sub>, R<sub>4</sub>', R<sub>7</sub>, and R<sub>7</sub>' at various positions.

R<sub>1</sub> and R<sub>1</sub>' independently represent H, OH, a 1-4 carbon alkyl, alkoxy or hydroxyalkyl group;

$R_4$  and  $R_4'$  independently represent H, OH; and

23. (Original) The method of claim 22, wherein the reversible competitive inhibitor is a compound selected from the group consisting of 1-deoxygalactonojirimycin,  $\alpha$ -*allo*-homonojirimycin,  $\alpha$ -*galacto*-homonojirimycin,  $\alpha$ -1-C-butyl-deoxynojirimycin, calystegine A<sub>3</sub>, calystegine B<sub>2</sub>, N-methyl-calystegine A<sub>3</sub>, and N-methyl-calystegine B<sub>2</sub>.

25. (Withdrawn) The method of claim 21, wherein the reversible competitive inhibitor is a compound of the following formula:



wherein  $R_0$  represents H or a  $C_1$ - $C_{12}$  alkyl chain;

$R_0'$  represents H, a straight chain or branched saturated carbon chain containing 1-12 carbon atoms, optionally substituted with a phenyl, hydroxyl or cyclohexyl group;

$R_1$  and  $R_1'$  independently represent H, OH, a 1-4 carbon alkyl, alkoxy or hydroxyalkyl group; and

$R_2$  and  $R_2'$  independently represent H, OH or a  $C_1$ - $C_{12}$  alkyl group.

26. (Withdrawn) The method of claim 25, wherein the reversible competitive inhibitor is a compound selected from the group consisting of isofagomine, N-dodecyl-isofagomine, N-nonyl-isofagomine, N-dodecyl-deoxynojirimycin, calystegine A<sub>3</sub>, calystegine B<sub>2</sub>, calystegine B<sub>3</sub> and calystegine C<sub>1</sub>.

27. (Withdrawn) The method of claim 26, wherein the reversible competitive inhibitor is isofagomine.

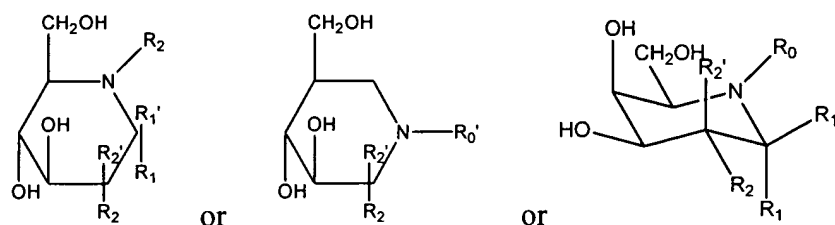
28. (Withdrawn) The method of claim 26, wherein the reversible competitive inhibitor is N-dodecyl-isofagomine.

29. (Previously presented) A method of improving treatment in an individual being administered a therapeutic vector comprising a gene encoding a protein, comprising co-administering to the individual an active site-specific chaperone for the protein.



36. (Original) The method of claim 35, wherein the reversible competitive inhibitor is 1-deoxygalactonojirimycin.

37. (Withdrawn) The method of claim 33, wherein the reversible competitive inhibitor is a compound of the following formula:



wherein  $\text{R}_0$  represents H or a  $\text{C}_1\text{-C}_{12}$  alkyl chain;

$\text{R}_0'$  represents H, a straight chain or branched saturated carbon chain containing 1-12 carbon atoms, optionally substituted with a phenyl, hydroxyl or cyclohexyl group;

$\text{R}_1$  and  $\text{R}_1'$  independently represent H, OH, a 1-4 carbon alkyl, alkoxy or hydroxyalkyl group; and

$\text{R}_2$  and  $\text{R}_2'$  independently represent H, OH or a  $\text{C}_1\text{-C}_{12}$  alkyl group.

38. (Withdrawn) The method of claim 37, wherein the reversible competitive inhibitor is a compound selected from the group consisting of isofagomine, N-dodecyl-isofagomine, N-nonyl-isofagomine, N-dodecyl-deoxynojirimycin, calystegine  $\text{A}_3$ , calystegine  $\text{B}_2$ , calystegine  $\text{B}_3$  and calystegine  $\text{C}_1$ .

39. (Withdrawn) The method of claim 38, wherein the reversible competitive inhibitor is isofagomine.

40. (Withdrawn) The method of claim 38, wherein the reversible competitive inhibitor is N-dodecyl-isofagomine.